REMARKS

The Office Action dated March 29, 2006 has been carefully reviewed and the foregoing remarks are made in response thereto. In view of the above amendments and following remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

By this Amendment, claims 1-17 have been amended. Support for amendment to claim 1 can be found on page 23, paragraph [0078]. Support for the amendment of claim 10 can be found at page 12, paragraph [0044]. New claims 20-22 are supported at page 25, paragraph [0084]+. Applicants respectfully submit that no new prohibited matter has been introduced by the amendments to the claims.

Upon entry of this amendment, claims 1-22 will be pending in the application, of which claims 18-19 are withdrawn from consideration. In view of the amendments, Applicants respectfully request the objections and rejections be withdrawn.

Summary of Office Action

1. Claims 1-17 are rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter.

2. Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

3. Claims 1-5, 9-14 and 16-17 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Mendrick *et al.* (WO 02/10453).

4. Claims 1-3, 6-7, 9 and 13-17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537, 1999) in view of Lindon (Progress in Nuclear magnetic Res. Spectroscopy, 39:1-40, 2001, and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001).

5. Claims 4 and 8 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286, 531-537 , 1999) in view of Lindon (Progress in Nuclear magnetic Res. Spectroscopty, 39:1-40, 2001, and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001), and further in view of James *et al.* (J. of the Royal Statistical Society Series, B 63:533-550).

6. Claim 5 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537 , 1999) in view of Lindon (Progress in Nuclear magnetic Res. Spectroscopty, 39:1-40, 2001, and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001) and further in view of MacGregor *et al.* (Toxicological Science, 59:17-36).

7. Claims 1-3, 6-7, 9 and 13-17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537 , 1999) in view of Lindon (Progress in Nuclear magnetic Res. Spectroscopty, 39:1-40, 2001, and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001), and further in view of Mendrick *et al.* (WO 02/10453).

8. Claim 15 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Mendrick *et al.* (WO 02/10453) in view of Shao *et al.* (J. Am. Statist. Assoc., 66:486-494).

Claim Objections

Claims 2-17 are objected to because the Examiner is of the opinion that dependent claims 2-17 should recite "the method of claim..." In response, claims 2-17 have been amended as requested by the Examiner. Reconsideration and withdrawal of this objection is respectfully requested.

Claim Rejections-35 U.S.C. § 101

Claims 1-17 are rejected under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. The Examiner asserts that "the claims do not recite tangible expression (*i.e.*, a real-world result) of analyzed gene expression data, nor any recitation of an actual (*i.e.*, concrete) result in a form useful to one skilled in the art." [Emphasis added.] Applicants respectfully traverse this rejection.

According to the Examiner, the US Patent Office current standards for determining subject matter eligibility under 35 U.S.C. § 101 is set forth in the Interim Guidelines at 1300 O.G. 4 (22 November 2005). The discussion in the Guidelines with regard to tangible results is found at pages 21-22. Under the heading "Tangible Result," the Guidelines state that the "tangible result" requirement does not necessarily mean that a claim must either be tied to a particular machine or apparatus or must operate to change articles or materials to a different state

or thing. The "tangible result" requirement merely requires that a method claim, expressly or inherently, produce a result that is useful, concrete and tangible. The Guidelines further specify that opposite meaning of "tangible" is "abstract."

Applicants respectfully assert the methods as claimed in the present invention meet the tangible result requirement set forth in the Guidelines. Although claims 1-17 recite a linear discriminate metric means to analyze gene expression data, they by no means recite an abstract idea or law of nature. The claims provide a practical application, *i.e.*, a method of identifying one or more marker genes whose level of expression predicts a biological response in a cell or tissue. For example, paragraph [0076] at page 22 of the specification teaches that markers obtained from gene expression analysis by a linear discriminate metric as claimed can be used as predictive tools for predicting toxic responses in cells or tissues. In light of the teachings of the specification, Applicants submit that gene expression analysis by linear discriminate metric is not mere output of the calculation of the LDA equation but has real world applications. The methods of the present invention provide, as an example. immediate benefit to a toxicologist who would otherwise conduct toxicological studies in animals to determine the toxicity of certain compounds. As such, Applicant submits the methods recited in claims 1-17 do produce a tangible result.

Applicants also respectfully submit that step (b) in the pending claims is combined with amended step (a) which recites that the "obtaining" is by "by at least one hybridization assay." As such, the pending claims all contain an active step of performing at least one hybridization assay. For example, the specification at paragraph [0078] defines the phrase "hybridization assay" as including various assay formats involving hybridization of nucleic acids, including hybridization of labeled nucleic acids on a microarray and various PCR reactions.

For the reasons discussed above, Applicants respectfully request the § 101 rejection be withdrawn.

Claim Rejections-35 U.S.C. § 112, Second Paragraph

Claims 1-17 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particular point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner has rejected claim 1 on the basis that the phrase "analyzing the gene expression data to identity...marker genes," is not clear as to whether the limitation "to identify" or "thereby identifying" is intended to be an active, positive method step. Furthermore, the Examiner alleges that the relationship between the preamble and the method step is not clear.

Applicants respectfully submit that the limitation "to identify" or "thereby identifying" one or more marker genes does recite active, positive steps. These steps include "obtaining gene expression data," "analyzing the expression date," and "predicting a toxic response." The relationship between the preamble and the method step is also clear. By following the steps of obtaining and analyzing gene expression data, one skilled in the art is able to arrive at the end result recited in the preamble. For these reasons, Applicants respectfully submit that claim 1 meets the requirement of §112, second paragraph. Applicants respectfully request the rejection be withdrawn.

Claim 10 is also rejected because the Examiner believes there is no antecedent basis for the terms "the samples of group 1" and "the samples of group 2." Without conceding the correctness of the Examiner's argument, claim 10 has been amended to recite "wherein "group 1 refers to the test group and group 2 refers to the control group." Support for the amendment can be found at page 12, paragraph [0044] of the specification.

Claim 10 is also rejected because the Examiner believes that it is unclear whether "the discriminate score for sample Z" is intended to be the "the discriminate score for each gene" or a different discriminate score. Applicants respectfully submit that claim 10 depends from claim 9 and thus carries all the limitations of claim 9, *i.e.*, the discriminate score for each gene.

Claim 10 is also rejected as the Examiner contends that there is insufficient basis for the limitation "variance" because claims 1 and 9 from which claim 10 depends do not recite "variance." Applicants respectfully submit that the term "variance" in claim 10 does have antecedent basis in claims 1 and 9. Claim 1 recites that the gene expression data is analyzed by a linear discriminate metric and claim 9 recites that the linear discriminate metric method comprises a scoring function. Claim 10 subsequently recites the specific scoring function containing various parameters such as the means and variances. Because the means and variances are elements that define the statistic equation of fl(z), they have antecedent basis in the

equation itself and in claim 9, which recites the scoring equation. Applicants respectfully request the rejection be withdrawn.

Claim 11 is rejected because the Examiner is unclear as to whether "a discriminate score for each gene" is intended to be different from "a discriminate score," As discussed above, there is no difference between the phrases "a discriminate score for each gene" and "a discriminate score." Therefore, claim 11 refers to "a discriminate score for each gene."

Claim 12 is rejected because the Examiner believes that it is unclear which "discriminate score" is intended in claim 12. Applicants respectfully submit the same argument for claim 11 applies to claim 12.

Claim 12 is also rejected because the Examiner asserts that the parameters "fl; X_i; Y_jl i-1...t; j=1...n" are not expressly defined either in the claims or in the specification. Applicants respectfully submit that these parameters are fully described in the specification. The Examiner' attention is directed to page 12, paragraph [0045] of the specification where definitions of parameters of fl; X_i; Y_jl i-1...t; j=1...n can be found. Applicants respectfully request the rejection be withdrawn.

Claim Rejections-35 U.S.C. § 102(e)

Claims 1-5, 9-14 and 16-17 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Mendrick *et al.* (WO 02/10453).

Applicants respectfully submit that WO 02/10453 was actually filed on July 31, 2001, and is identical in content to U.S. Application Serial No. 09/917,800, also filed on July 31, 2001, from which the instant application claims priority under 35 U.S.C. § 120. Applicants provide herewith as Exhibit A, the PCT filing request for WO 02/10453 dated July 31, 2001 and the return receipt postcard form the U.S. receiving office stamped July 31, 2001. Accordingly, the international file date on the front page of the published PCT appears to be a typographical error. As such, WO 02/10453 is not prior art under 35 U.S.C. § 102(e) and Applicants respectfully request withdrawal of the rejection.

Claim Rejections-35 U.S.C. § 103(a)

Claims 1-3, 6-7, 9 and 13-17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537, 1999) in view of Lindon (Progress in Nuclear magnetic Res. Spectroscopy, 39:1-40, 2001), and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001). Applicants respectfully traverse the rejection.

Applicants respectfully submit that nothing in Golub suggests the use of LDA to analyze gene expression and the Examiner recognizes this as evidenced by the admission on page 8, last paragraph.

The Examiner asserts that Lindon *et al.* teach application of a linear discriminate method to pattern recognition and that it would have been obvious to use such a method combined with the teachings of Golub. The Examiner further asserts that Lindon *et al.* "disclose differential gene expression as a result of disease or toxicity" (page 9 of the office action). A careful review of the Lindon reference reveals that the reference, in fact, does not teach the use of LDA method to analyze gene expression. Instead, the reference is directed to analysis of small molecule metabolites in a biofluid with magnetic resonance techniques. Although Lindon *et al.* disclose gene expression analysis at page 3 as a means to study genetic modification, disease or xenobiotic toxicity, they favor other means of genetic modification, disease or xenobiotic toxicity studies over gene expression analysis because "relationships between gene regulation/expression and the integrated function and control of cellular systems are still far from clear" and because "[t]he the lack of understanding of the biological consequences of altered gene expression has led to the development of proteomics," which the magnetic resonance technology may apply. Thus. it is clear that Lindon *et al.* do not teach the use of LDA to analyze gene expression patterns and actually teach away from a combination of such methodologies. As such, the pending rejections should be withdrawn. See MPEP § 2145.

Further, for *prima facie* obviousness to be established, there must be a reasonable expectation of success. Applicants respectfully submit that Lindon's own teachings specifically call into question the use of gene expression analysis and deny that such an expectation exists. Therefore, it would not be obvious to one skilled in the art to combine Lindon's teaching with the teachings of Golub and Xiong of gene expression analysis to arrive at the present invention. Applicants therefore respectfully traverse the rejection and request its reconsideration and withdrawal.

Claims 4 and 8 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537 , 1999) in view of Lindon *et al.* (Progress in Nuclear magnetic Res. Spectroscopty, 39:1-40, 2001), and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001), and further in view of James *et al.* (J. of the Royal Statistical Society Series, B 63:533-550).

The teachings and deficiencies of Golub *et al.*, Xiong *et al.*, and Lindon *et al.* are discussed above and Applicants respectfully submit that this discussion is also pertinent to this rejection under 35 U.S.C. § 103(a). Applicant submits that James *et al.* is unable to cure the deficiencies of the primary references because James *et al.* do not teach or suggest application of their FLDA (functional Linear Discriminant Analysis) methodology to gene expression analysis, let alone analysis of cells or tissues exposed to toxins as in claim 2. Thus, this alleged prior art supplies no motivation to one of ordinary skill to combine the teachings of these references in the precise manner required to arrive at the invention recited in claims 4 and 8.

Claim 5 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537 , 1999) in view of Lindon (Progress in Nuclear magnetic Res. Spectroscopty, 39:1-40, 2001, and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001) and further in view of MacGregor *et al.* (Toxicological Science, 59:17-36). The Examiner asserts that although Golub, Lindon, Xiong do not disclose hepatotoxicity, MacGregor *et al.* do. Applicants respectfully traverse this rejection.

The teachings and deficiencies of Golub *et al.*, Xiong *et al.*, and Lindon *et al.* are discussed above. Like Golub *et al.* and Xiong *et al.*, MacGregor *et al.* do not teach LDA analysis. Although Lindon *et al.* teach LDA analysis, they teach away gene express based functional analysis and thus do not provide motivation to combine with the teachings of Golub *et al.*, Xiong *et al.*, and MacGregor *et al.*, whose methods of tumor or cancer classification and hepatotoxicity prediction are all based on gene expression analysis.

Claims 10-13 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Golub *et al.* (Science, 286:531-537 , 1999) in view of Lindon *et al.* (Progress in Nuclear magnetic Res. Spectroscopty, 39:1-40, 2001), and further in view of Xiong *et al.* (Mol. Genet. and Metabolism, 73: 239-247, 2001), and further in view of Mendrick *et al.* (WO 02/10453).

Claim 15 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Mendrick *et al.* (WO 02/10453) in view of Shao *et al.* (J. Am. Statist. Assoc., 66:486-494).

Applicants respectfully traverse these rejections. Applicants note that both rejections are based on Mendrick *et al.* As discussed in the above 102(e) rejection, the WO 02/10453 publication is not prior art against the instant claims. Accordingly, withdrawal of these rejections is appropriate.

CONCLUSIONS

Applicants respectfully submit that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should any issues remain.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-1283. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

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Dated: Sept 29, 2006

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